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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/914,046	10/01/2001	Liang Xu	2474.0010001/BJD/JKM	8537

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EXAMINER	
DIBRINO, MARIANNE NMN	
ART UNIT	PAPER NUMBER
1644	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/914,046	XU ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7,8,12,69,73,75 and 76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7,8,12,69,73,75 and 76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 6/14/07.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed 5/7/07 is acknowledged and has been entered.

2. Applicant is reminded of Applicant's election with traverse of Group II, and species of immunoliposome comprising a pre-linked antibody fragment that binds a transferrin receptor and further comprises DNA encoding wild type p53 in Applicant's responses filed 8/27/04 and 4/30/04. Group I had been rejoined to Group II.

Claims 1-4, 7, 8, 12, 69, 73, 75 and 76 are currently being examined.

3. For the purpose of prior art rejections, the filing date of the instant claims 1-4, 7, 8, 12, 69, 73, 75 and 76 is deemed to be the filing date of PCT US00/04392, *i.e,* 2/22/00, as the parent provisional application 60/121,133 does not support the claimed limitations of the instant application. The said limitations are those of the ratios recited at the last 3 lines of claim 1 and "MPB" in claim 8.

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1, 3, 7, 8, 12, 73, 75 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,248,721 B1 in view of Yu *et al* (Oncogene 11: 1383-1388, 1995, of record), US 2001/0008759 A1 (of record), US 6,448,390 B1, Wright and Huang (Biochim. Biophys. Acta. 1992, 1103: 172-178, of record) and Morishige *et al* (Biochim. Biophys. Acta. 1993, 1151: 59-68, of record).

US 6,248,721 B1 discloses that cationic liposomes have proven to be a safe and effective means for inducing the transient expression of DNA in target cells. US 6,248,721 B1 discloses that cationic liposomes, such as for example DOTAP/DOPE, and ligand targeted cationic liposomes are employed for the delivery of plasmid-DNA encoding a protein(s), the ligand-targeted liposomes made by covalently attaching ligands or antibodies to the surface of the cationic liposome. US 6,248,721 B1 discloses using monoclonal antibodies such as mAb HMSA5 against melanoma-specific surface antigens when melanoma tumor cells are to be targeted. US 6,248,721 B1 discloses that the DNA is formed into a complex with the preformed cationic liposomes using standard methodology or alternatively the DNA is encapsulated into the liposome interior. US 6,248,721 B1 discloses that the DNA containing liposomes are then used to transfer the DNA to tumor cells *in vivo* by direct intra-tumor injection or *in vitro (*using freshly explanted tumor cells) followed by return of the transduced cells to the recipient (column 50 at lines 9-40).

US 6,248,721 B1 does not disclose making the nucleic acid-cationic immunoliposome by directly conjugating an anti-Her2/neu scFv antibody fragment to said liposome within the ratio range recited in instant base claim 1 followed by mixing the resulting cationic immunoliposome with said nucleic acid.

Yu *et al* teach that cationic liposome-mediated E1A (*i.e,* a tumor suppressor) gene (DNA) transfer, *i.e.,* in a pharmaceutical composition, significantly inhibited growth and dissemination of ovarian cancer cells that over-express HER-2/neu in treated mice. Yu *et al* further teach using a DNA: liposome ratio of 1:13, a ratio that is within the range that is recited in instant claim 1. Yu *et al* teach making cationic liposomes that can be targeted to tumors that overexpress p185 by incorporating into the liposomes anti-p185 antibodies against the HER-2/neu-encoded p185 receptor (especially abstract, page 1385 at column 1 at the first full paragraph, page 1387 at column 1 at the first full paragraph). With regard to the order of the method steps recited in claim 1, Yu *et al* teach addition of the antibody to the liposome, not to the liposome:DNA complex. Yu *et al* teach that the cationic liposome consists of DC-cholesterol and DOPE present at a 3:2 ratio (page 1385 at the first full paragraph).

US 2001/0008759 A1 discloses targeting of ErbB2 (*i.e,* HER-2/neu)-overexpressing cells has been accomplished primarily using anti-ErbB2 antibodies in different formats, including conjugation to liposomes containing chemotherapeutics ([0004]).
US 2001/0008759 A1 discloses that for liposomal targeting, antibodies should be used that bind specific epitopes and that are subsequently rapidly internalized and yield a functional targeting vehicle ([0005]). US 2001/0008759 A1 discloses that preferred antibodies include scFv antibodies ([0020]). US 2001/0008759 A1 discloses that to facilitate coupling of the purified scFv to liposomes, the C6.5 gene (anti-c-ErbB2 or anti-HER-2/neu scFv) was subcloned into an *E. coli* expression vector resulting in addition of a free cysteine residue at the C-terminus of the scFv, *i.e.,* the said free cysteine residue contains a sulfhydral group at the carboxy terminus of the antibody fragment, and that use of the immunoliposomes with the scFv targeting antibodies *in vivo* was more effective than use of untargeted liposomes ([0206]).

US 6,448,390 B1 discloses cationic liposomes such as DOTAP/DOPC/DOPE containing MPB-PE can be directly conjugated to thiolated protein(s), *i.e.,* conjugation occurs via a sulfur atom which was part of a sulfhydral group at the carboxy terminus of the protein prior to said conjugation (especially Example 13). US 6,448,390 B1 further teaches scFv antibodies, and their use in a chimeric protein as a delivery vehicle (column 21 at lines 2-13).

Wright and Huang teach that MPB-PE was effective at stabilizing the bilayer phase of DOPE in liposomes. Wright and Huang teach that antibody can be attached to liposomes through covalent or non-covalent attachment to derivatized membrane phospholipids such as conjugation of thiolated antibody to preformed liposomes containing MPB-PE, and that such method facilitates proper orientation of the antibody and avoids the use of detergent that is employed with acylated antibody. Wright and Huang teach that conjugation of antibody to PE-based liposomes using this strategy may produce target sensitive immunoliposomes (especially abstract, first full paragraph on page 173 at column 1).

Morishige *et al* teach conjugating Fab' fragments with liposomes containing MPB-PE (PC:Cholesterol:MPB-PE in 10:10:1 molar ratio), and mixing 1 mg Fab' per 6 umol of PC (*i.e,* 1 mg Fab' with 7,475.4 ug of liposome lipid (or a 1:7.5 ratio of antibody fragment to lipid on a weight:weight basis). Morishige *et al* teach that although they prepared immunoliposomes with two antibodies, there is no experimental evidence that the 2-step targeted immunoliposome is more effective *in vivo* than the conventional 1-step immunoliposome, and that an advantage of using the 2-step system is that if the first antibody is available in purified form, one does not have to purify the second antibody that is the targeting antibody (especially abstract, materials and methods at the paragraph spanning columns 1-2 on page 6, paragraph spanning columns 1-2 on page 61, paragraph spanning pages 66-67).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a cationic immunoliposome comprising DOTAP/DOPE and pharmaceutical composition thereof as disclosed by US 6,248,721 B1 and further comprising MBP-PE as disclosed for the cationic liposome of US 5,448,390 B1 and to have directly conjugated an scFV antibody fragment to said cationic liposome, the said scFv having a carboxy-terminal cysteine and specificity of anti-HER-2/neu disclosed by US 2001/0008759 A1, the MBP-PE stabilizing the bilayer phase of DOPE as taught by Wright and Huang and the ratio of scFV-cysteine antibody fragment to lipid determined on a weight to weight basis for the scFV-cysteine based upon its molecular weight as compared to that of the Fab' fragment used by Morishige *et al* in creating their targeted liposome containing MPB-PE, and further to have incorporated DNA for delivery to tumor cells as disclosed by US 6,248,721 B1 at the ratio taught by Yu *et al*, including for DNA encoding a tumor suppressor gene such as E1A taught by Yu *et al*.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to make a targeted cationic liposome containing a DNA therapeutic agent capable of targeting said immunoliposome to a Her 2/neu expressing tumor and delivering a tumor suppressor gene to said tumor because: (1) US 6,248,721 B1 discloses that cationic liposomes, including for instance ones comprising DOTAP/DOPE, have proven to be a safe and effective means for inducing the transient expression of DNA in target cells, that the ligand-targeted liposomes are made by covalently attaching ligands or antibodies, such as with specificity for a tumor antigen, to the surface of the cationic liposome, that DNA may be formed into a complex with the preformed cationic liposomes or alternatively encapsulated into the interior of the liposome, and that the resulting targeted cationic immunoliposomes are used to transfer DNA to tumor cells *in vivo* by direct intra-tumor injection or *in vitro* into freshly explanted tumor cells; (2) Yu *et al* teach that cationic liposome-mediated E1A (*i.e,* a tumor suppressor) gene (DNA) transfer significantly inhibited growth and dissemination of ovarian cancer cells that over-express HER-2/neu in treated mice and the ratio of DNA to liposome (ug: nmol) that is used, and teach attaching an anti-Her2/neu-encoded-p185-receptor antibody to said liposome prior to mixing with DNA in order to target to Her-2/neu expressing tumor cells; (3) US 6,448,390 discloses that cationic liposomes, such as for instance those comprising DOTAP/DOPE/DOPC and further comprising MPB-PE can be directly conjugated to thiolated proteins via a sulfur atom which was part of a sulfhydral group at the carboxy-terminus of the protein prior to said conjugation; (4) US 2001/0008759 A1 discloses anti-Her2/neu scFv-cys antibody fragments conjugated to liposomes containing chemotherapeutic agents for treating cancer, the cysteine being a sulfhydral containing group at the carboxy-terminus of the protein, the scFv-cys-targeted liposome being more effective than untargeted liposomes; (5) Morishige *et al* teach a coupling ratio of ug of antibody with a free SH group at the carboxy-terminus (part of Cys) to use per umol of lipid when conjugating Fab' antibody fragments with liposomes containing MPB-PE; (6) OSA was aware of the molecular weights of Fab' vs scFV fragments; (7) Wright and Huang teach attachment of thiolated antibody to preformed liposomes containing MPB-PE, and that such method facilitates proper orientation of the antibody and avoids the use of detergent that is employed with acylated antibody.

Applicant's arguments with regard to the references previously cited in this rejection have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 5/7/07 on pages 6-15.

It is the Examiner's position that: (1) Yu *et al* is being argued separately by Applicant; (2) Applicant's assertion that Yu *et al* admits that targeted liposomes could only be prepared once a ligand for the HER-2/neu-encoded p185 receptor becomes available is a mischaracterization. Yu *et al* teach "...designing liposomes that can target the E1A gene to tumors that over-express p185 by incorporating into liposomes anti-p185 antibodies or the ligand for the HER-2/neu-encoded receptor (when it becomes available)", clearly indicating that anti-p185 antibodies were known and available, but the ligand for the HER-2/neu-encoded p185 receptor was not available. In addition, it was routine in the art at the time the invention was made to produce antibodies; (3) Wright and Huang are being argued separately with regard to the attachment of antibodies to MPB-PE lipids; (4) With regard to Applicant's arguments to Morishige that Fab' fragments are much larger molecules than scFvs so there is no reason to believe that the same ratios could be utilized in the preparation of scFv-comprising immunoliposomes, Morishige *et al* teach a mg Fab' to umol of lipid ratio that can be converted to a w:w ratio and one of ordinary skill in the art was aware of the molecular mass of both antibody fragments and could adjust the ratio accordingly for a different antibody fragment; (5) US 2001/0008759 A1 is being argued separately with regard to the manner of conjugation of the scFv to liposomes and the nature of the liposomes, and other art references cited herein teach conjugation of antibody or protein to MBP-PE-containing cationic liposomes; (6) US 6,248,721 B1 discloses that the DNA can be either complexed with the cationic liposome or it can be incorporated into the cationic liposome, and the antibody or ligand can be covalently attached to the cationic liposome; (7) with regard to Applicant's attached copy of Li and Huang, not cited in the instant rejection, although Li and Huang discuss difficulty in tissue-specific gene delivery, US 6,248,721 B1, that is cited in the instant rejection, discloses direct intra-tumoral injection of the targeted cationic liposome *in vivo* or *in vitro*; (8) with regard to Applicant's attached copy of Li and Huang, not cited in the instant rejection, although Li and Huang discuss that DNA is a large molecule with a large hydrodynamic diameter as compared with a chemotherapeutic drug and Applicant's assertion that OSA would not have predicted that additional molecules such as antibodies or antibody fragments could be added to the liposomes, US 6,248,721 B1, that is cited in the instant rejection, discloses covalently attaching ligands or antibodies to the surface of the cationic liposome that will also further comprise a desired DNA.

6. Claims 2, 4 and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 6,248,721 B1 in view of Yu *et al* (Oncogene 11: 1383-1388, 1995, of record), US 2001/0008759 A1, US 6,448,390 B1, Wright and Huang (Biochim. Biophys. Acta. 1992, 1103: 172-178) and Morishige *et al* (Biochim. Biophys. Acta. 1993, 1151: 59-68) as applied to claims 1, 3, 7, 8, 12, 73, 75 and 76 above, and further in view of Xu *et al* (Human Gene Therapy: 467-475, 1997, IDS reference) and U.S. Patent No. 6,200,956 B1 (of record).

US 6,248,721 B1, US 2001/0008759 A1, Yu *et al*, Wright and Huang and Morishige *et al* have all been discussed above, hereafter referred to as "the combined references."

The combined references do not teach wherein the liposome comprises an antibody fragment that is capable of binding to a transferrin receptor and a nucleic acid that encodes a wild type p53.

Xu *et al* teach transferrin-cationic liposomes mixed with DNA encoding wild type p53, at a nucleic acid/lipid ratio of 1 ug DNA to 8 nmol lipid, a ratio that is within the range recited in instant claim 1. Xu *et al* teach use of the nucleic acid transferrin-cationic liposomes are effective for transfection of tumor cells, administration results in significant inhibition of tumor growth and prevents relapse and metastasis of mammary tumors in nude mice, and for treatment of head and neck cancer.

U.S. 6,200,956 B1 discloses immunoliposomes, including cationic polymers of cationic lipids, chemically coupled, covalently or non-covalently, to a ligand of a membrane receptor present at the surface of a target cell type, such as a tumor cell. U.S. 6,200,956 B1 discloses immunoliposomes further comprising DNA that is to be delivered to the said target cell type, *i.e,* is a nucleic acid-cationic immunoliposome complex, and pharmaceutical compositions thereof. US 6,200,956 B1 discloses that transferrin and antibodies/fragments of antibodies are ligands of the target cell surface molecule transferrin, *i.e,* are targeting molecules for cells such as tumor cells, and further discloses pharmaceutical compositions are targeting molecules for cells such as tumor cells (especially column 1 at lines 63-67, column 2 at lines 1-15 and 26-33 and column 4 at lines 20-64).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a targeted cationic immunoliposome such as the one disclosed by the combined references, but using DNA encoding wild type p53 and at the ratio of DNA-lipid taught by Xu *et al* in their transferrin-cationic liposome and substituting for said transferrin another transferrin receptor specific ligand, the antibody fragment specific for the transferrin receptor disclosed by U.S. 6,200,956 B1 in the form of scFv-cys taught by the combined references.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to treat cancer of the head and neck more effectively using a cationic immunoliposome because: (1) The combined references teach an scFv-cys-targeted nucleic acid-cationic immunoliposome complex as enunciated supra, (2) U.S. Patent No. 6,200,956 B1 discloses using scFv or Fab' antibody fragments linked to effector cationic lipid nucleic acid complexes provides the ability to conveniently customize the complex for delivery to specific cells and tissues such as tumor cells, (3) Xu *et al* teach using a transferrin-targeted immunoliposome with the effector molecule wild-type p53 is useful for treatment of head and neck cancer, (4) U.S. Patent No. 6,200,956 B1 discloses that transferrin and anti-transferrin receptor antibodies or antigen binding fragments thereof are ligands of the target cell surface transferrin receptor, (5) the scFv fragments disclosed/taught by U.S. Patent No. 6,200,956 B1 has the art disclosed advantage of being more effective for penetrating tumor tissue

Applicant's arguments with regard to the references previously cited in this rejection have been fully considered, but are not persuasive.

Applicant's arguments are of record in the amendment filed 5/7/07 on pages 20-22.

It is the Examiner's position that: (1) the Xu *et al* and U.S. Patent No. 6,200,956 B1 references are being argued separately; (2) the Examiner's arguments set forth above at item "5" of this Office Action apply herein with regard to the other references cited in the instant rejection.

7. No claim is allowed.

8. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Christina Y. Chan, can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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